ACUTE KIDNEY INJURY

Immune networks in CI-AKI

The underlying mechanisms leading to contrast-induced acute kidney injury (CI-AKI) are unclear. New findings demonstrate that CI-AKI involves a coordinated response between resident and infiltrating renal phagocytes and requires the tubular reabsorption of contrast media via the brush border enzyme dipeptidase 1. "One of the most important findings was the identification of the receptor that regulates the uptake of toxins from urine," explains researcher Daniel Muruve. "These findings highlight the ability of the kidney to sample molecules filtered into the tubule and present them to the immune system."

Following the observation that contrast induces an inflammatory response, Muruve and colleagues assessed the role of the immune sensor NLRP3 in CI-AKI. Administration of ioversol induced kidney injury in volume-depleted control mice, but *Nlrp3*$^{-/-}$ mice were protected from CI-AKI. Multiphoton intravital microscopy of reporter mice expressing GFP on cells of the myeloid lineage demonstrated the recruitment of GFP^{+} leukocytes before the onset of kidney injury in control, but not in *Nlrp3*$^{-/-}$, mice. Interestingly, administration of contrast agent to cultured tubular epithelial cells caused cell death via a mechanism that was not dependent on NLRP3. Further studies demonstrated that rather than inducing tubular epithelial cell apoptosis, contrast-induced activation of the NLRP3 inflammasome occurred primarily in leukocytes, triggering an immune response.

To explore the mechanisms by which the kidney handles contrast, the researchers performed intravital microscopy imaging, demonstrating that contrast is rapidly taken up by resident phagocytes within the kidney. In volume depleted mice, contrast was also reabsorbed by tubular epithelial cells coinciding with leukocyte recruitment, with evidence of leukocytes actively taking up contrast material from epithelial cells before migrating away. "Our study highlights the importance of the kidney immune system in regulating injury," notes Muruve. "Better understanding the interactions between resident and recruited immune cells with renal cells will open up new potential pathways for drug discovery specifically for kidney disease."

Susan J. Allison

ORIGINAL ARTICLE Lau, A. et al. Renal immune surveillance and dipeptidase-1 contribute to contrast-induced acute kidney injury. *J. Clin. Invest.* https://doi.org/10.1172/JCI96640 (2018)

NEPHROTIC SYNDROME

RHO-like GTPases in nephrotic syndrome

Nephrotic syndrome (NS) is usually treated with steroids, although steroid-resistant forms of NS exist. The mechanism of this steroid resistance is unclear, but now six novel genes mutated in NS have been identified by whole-exome sequencing and linkage analysis in 17 families with partially treatment-sensitive NS.

"We demonstrate that the six gene products physically or functionally interact and delineate two novel complexes that regulate the activity of RHO-like GTPases in NS and that are apparently sensitive to steroid treatment," says Friedhelm Hildebrandt. The researchers showed that CDK20, MAGI2 and TNS2 interact with the RHOA GTPase-activating protein DLC1 to regulate the activity of RHOA. *MAGI2*, *TNS2* and *CDK20* overexpression or *DLC1* knockdown in HEK293T cells increased active RHOA levels, whereas *MAGI2*, *TNS2* and *CDK20* knockdown or *DLC1* overexpression reduced active RHOA levels. Notably, the effects of *DLC1* or *CDK20* (but not *MAGI2* or *TNS2*) knockdown on active RHOA levels were reversed by steroid treatment. Importantly, *MAGI2*, *CDK20* or *DLC1* knockdown in human podocytes reduced their migration rate in vitro, suggesting that the pathogenic effects of NS mutations in this RHOA-regulatory module might occur through podocyte dysfunction.

Finally, the guanine nucleotide exchange factors ITSN1 and ITSN2 were shown to modulate the activity of the RHO-like GTPase CDC42 and regulate filopodia formation in human podocytes in vitro. Additionally, in the lipopolysaccharide (LPS) model of transient NS, recovery from podocyte injury was delayed in ITSN2-deficient mice compared with that in wild-type mice, suggesting that CDC42 is involved in the pathogenesis of NS.

"Our findings should enable the generation of functional assays to identify therapeutic targets for steroid-resistant NS, for which no effective treatment currently exists," says Hildebrandt.

Grant Otto

ORIGINAL ARTICLE Ashraf, S. et al. Mutations in six nephrosis genes delineate a pathogenic pathway amenable to treatment. *Nat. Commun.* **9**, 1960 (2018)

DEVELOPMENT

Regulation of nephrogenesis

In mammalian kidneys nephrogenesis is completed before or shortly after birth and nephron number subsequently decreases throughout life. New data from Oded Volovelsky, Raphael Kopan and colleagues suggest a role of hamartin in determining initial nephron number. This protein, which is encoded by *Tsc1*, is an inhibitor of mammalian target of rapamycin (mTOR).

"A non-ideal environment of kidney development in the embryo or a disease of the kidney such as pyelonephritis or glomerulonephritis in childhood reduces the nephron reserve so significantly increases the risk of chronic kidney disease in adulthood," explains Volovelsky. "Our goal is to find a way to give children the best background to cope with kidney disease in adulthood resulting from diabetes, obesity and high blood pressure. This goal can be achieved by reducing risk factors for prematurity or malnutrition during pregnancy and by identifying the mechanisms that determine initial nephron numbers, which was the focus of our recent study."

The researchers show that in mice complete loss of mTOR in nephron progenitor cells (NPCs) resulted in failure to develop a functional kidney, whereas loss of one mTOR allele led to a significant decrease in nephron count. By contrast, NPC-specific deletion of *Tsc1* resulted in severe tubular lesions but normal glomeruli, whereas loss of one *Tsc1* allele prolonged nephrogenesis, leading to a significant increase in nephron number with no apparent adverse effects. The *Tsc1* phenotypes were dependent on the scaffold protein Raptor but independent of mTOR activity.

"Hamartin has an mTOR-independent role in determining the timing of cessation of nephrogenesis, and thus nephron number," concludes Kopan. "We are now trying to decipher the mechanism and hope to identify druggable targets to enable us to start marching on the long road leading to clinical interventions to maximize initial nephron numbers in premature babies and other at-risk populations."

Ellen Carney

ORIGINAL ARTICLE Volovelsky, O. et al. Hamartin regulates cessation of mouse nephrogenesis independently of Mtor. *Proc. Natl. Acad. Sci. USA* https://doi.org/10.1073/pnas.1712955115 (2018)